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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,868	10/24/2001	Rifat Pamukcu	P-168-1	8300

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EXAMINER
OWENS JR, HOWARD V

ART UNIT	PAPER NUMBER
1623	7

DATE MAILED: 08/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,868	PAMUKCU ET AL.	
	Examiner	Art Unit	
	Howard V Owens	1623	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Respons to Arguments

The following is in response to the amendment filed 6/12/03:

An action on the merits of claims 1-6 is contained herein below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

35 U.S.C. § 103

Applicant's arguments filed have been fully considered but they are not persuasive. The rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Nishi et al., U.S. Patent No. 5,998,437 in combination with Taylor et al., U.S. Patent No. 4,950,680, Earnest et al., Journal of Cellular Biochemistry, supplement 161:pp. 156-166 and Fang et al., Journal of Biological Chemistry, vol.272(23), pp. 14860-14866 is maintained for the reasons of record set forth below.

Claims 1-6 are drawn to a method of treating a mammal having a precancerous lesion, inhibiting neoplastic cells and regulating apoptosis comprising administering a pharmacologically effective amount of a fused pyrimidine compound of formula 1.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Nishi et al. teach fused pyridine inhibitors analogous to those set forth in the instant claims (see abstract and columns 2-16) and teach that these derivatives are selective inhibitors of cGMP phosphodiesterase (col. 1, line 41 - col.2, line 14). However, Nishi does not teach the treatment of precancerous lesions, the inhibition of neoplastic cells nor the regulation of apoptosis as uses for the compounds.

Fang et al. teach that a cGMP-phosphodiesterase inhibitor can induce apoptosis in cardiac myocytes (p. 14863) which adequately bridges the nexus between the use of compounds which have an inhibitory effect on cGMP-PDE as inducers of apoptosis.

Taylor et al. teach (col.3, line 43 - col. 4, line 55 and col. 5, lines 15-20) that tumor metastasis is enhanced by tumor cell interactions with platelets and that agents which block or prevent tumor cell-platelet interaction and aggregation such as inhibitors of TXA_2 synthetase and phosphodiesterase have antimetastatic effects; moreover, Earnest et al. teach that phosphodiesterases and cyclic cGMP kinases (and inhibitors thereof) may be central to cancer initiation and promotion (see abstract and pp. 157-159) which adequately bridges the nexus between the differences in the prior art and the invention as claimed.

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use a fused pyrimidine of formula I to treat precancerous lesions, inhibit neoplastic cells or regulate apoptosis.

A person of ordinary skill in the art would have been motivated to use the fused pyrimidines of formula I to treat precancerous lesions, inhibit neoplastic cells or regulate apoptosis as the prior art teaches that these compounds as inhibitors of TXA2 synthetase and phosphodiesterase have an anti metastatic effect through the inhibition of tumor cell induced platelet aggregation. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). One of skill in the art would have a reasonable expectation of success in the treatment of precancerous lesions with the fused pyrimidine compounds of the invention, or any compound for that matter which inhibits cGMP phosphodiesterase as the inhibition of this enzyme has been shown in the prior art to disrupt the cellular cascade from which certain neoplasms are formed.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by

combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the examiner set forth the teachings of Nishi et al. to establish the fact that applicant's compounds although not claimed as such nor set forth in the instant specification are in fact recognized as phosphodiesterase inhibitors in the prior art. Applicant can not discount the teachings of Nishi (when the same compounds of Nishi deemed as cGMP phosphodiesterase inhibitors are set forth in the instant invention) and simultaneously argue that prior art references which do not recite cGMP phosphodiesterase inhibition fail to support a basis of obviousness for the instant invention. If applicant admits that only prior art references which recite cGMP are appropriate, than Nishi is appropriate; additionally, applicant's specification is silent with regard to either cGMP/ cAMP phosphodiesterase activity and differentiation with respect to this compound in relation to anti-tumor or apoptotic activity, thus the issue of "impermissible hindsight reasoning" with regard to the use of Nishi et al. is moot since these teachings were gleaned outside of applicant's teachings. Moreover, if Nishi specifically mentioned or cited neoplasia as being affected by cGMP phosphodiesterase inhibitors than the claims would be rejected under 35 U.S.C. 102(b), not 103(a). All the elements of the claims need not be expressly taught in one reference to provide a basis of obviousness. The teachings of Taylor and Earnest were set forth to show the link in the prior art between phosphodiesterase inhibitors and tumor growth. Taylor teaches the use of phosphodiesterase inhibitors as agents which block or prevent tumor cell-platelet interaction and aggregation. Applicant's assertion that the teachings of Taylor are restricted to cAMP phosphodiesterase inhibitors is not convincing. Applicant has chosen the lone Figure correlating cAMP and phosphodiesterase to define the teachings as a whole. The bulk of Taylor teaches phosphodiesterase inhibitors broadly as agents which block or prevent tumor cell-platelet interaction and aggregation. No where in either Taylor or Earnest is it taught that the invention as a whole is limited to

"PD1" type inhibitors as applicant asserts. Moreover, one of skill in the art would have a reasonable expectation of success in the use of an agent or compound which is effective against tumors in the treatment of tumor growth for primary tumors. Earnest like Taylor has provided sufficient motivation for the nexus of phosphodiesterase inhibitors as effectors of tumor growth, as it teaches that "phosphodiesterases ..... may be central to cancer initiation and promotion".

The examiner maintains the position that a person of ordinary skill in the art would have been motivated to use the fused pyrimidines of formula I to treat precancerous lesions, inhibit neoplastic cells or regulate apoptosis as the prior art teaches that these compounds as inhibitors of TXA2 synthetase and phosphodiesterase have an anti metastatic effect through the inhibition of tumor cell induced platelet aggregation; moreover, that one of skill in the art would have a reasonable expectation of success in the treatment of precancerous lesions with the fused pyrimidine compounds of the invention, or any compound for that matter which inhibits cGMP phosphodiesterase as the inhibition of this enzyme has been shown in the prior art to disrupt the cellular cascade from which certain neoplasms are formed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600